

Amendments to the Specification

Please replace paragraph [0009] with the following amended paragraph:

[0009] Accordingly, iontophoresis, as well as other electrically induced techniques, such as electroporation, has been incorporated into many transdermal delivery devices, including the popular dermal patch. Therefore, there are many dermal patches known in the art today which incorporate a power source and electrical circuitry for aiding transdermal ~~transdermal~~ delivery.

Please replace paragraph [0012] with the following amended paragraph:

[0012] Bioelectrodes come in many sizes, shapes and configurations such as the following assigned to Ioimed, Inc., which produces iontophoretic delivery devices. Examples of such bioelectrodes include those disclosed in U.S. Pat. Nos. 5,037,380 and 5,248,295 which teach a patch having a refillable receptacle; U.S. Pat. No. 5,846,217 which teaches a patch having a small access window for refilling; and U.S. Pat. Nos. 5,374,245, 5,730,716 and 6,223,075 which teach a patch that holds a dry medicament and must be hydrated. All such bioelectrodes are complex and consist of many parts and are therefore relatively bulky. Accordingly, those that are incorporated into dermal patches cause the patches to be large and relatively expensive. Moreover, such dermal patches must be charged, or loaded, by a clinician and not by the subject.

Please replace paragraph [0023] with the following amended paragraph:

[0023] According to features in the described preferred embodiments the conductive fluid is a hydrogel.

Please replace paragraph [0031] with the following amended paragraph:

[0031] According to features in the described preferred embodiments the electric current serves for causing iontophoresis, ~~electrophoresis~~, electrophoresis, electroporation or any combination thereof.

Please replace paragraph [0033] with the following amended paragraph:

[0033] According to features in the described preferred embodiments the retainer is selected from the group consisting of a vessel, a tube, ~~a jar~~, a jar, a container, a dispenser and an ampoule.

Please replace paragraphs [0053] and [0054] with the following amended paragraphs:

[0053] According to a yet further aspect of the present invention there is provided a device for treatment of hyperhidrosis, the device including: a dermal patch including an electrochemical cell wherein the electrochemical cell is a flexible thin layer open liquid state electrochemical cell which includes a first layer of insoluble negative pole, a second layer of insoluble positive pole and a third layer of aqueous electrolyte, the third layer being disposed between the first and second layers and including: (a) a deliquescent material for keeping the open cell wet at all times; (b) an electroactive soluble material for obtaining required ionic conductivity; and (c) a water-soluble polymer for obtaining a required viscosity for adhering the first and the second layers to the third layer, having at least two electrodes positioned on one side of the dermal patch, the electrodes being for forming electrical contact with the skin portion of the subject; and the patch being designed and configured for delivering an electric current through the skin, the electric current being for delivery of ions into the skin portion of the subject and for treatment of ~~hyperhidrosis~~ hyperhidrosis.

[0054] According to a yet further aspect of the present invention there is provided an iontophoretic patch for transdermal or intradermal delivery of at least one substance, the patch including: an electrochemical cell for powering the patch; at least two electrodes in electrical contact with the electrochemical cell; and a conductive fluid, wherein the conductive fluid is preapplied to the at least two electrodes; and wherein on contacting the patch with skin an electric current is delivered through the conductive fluid and skin of a subject so as to ~~transdermally~~ transdermally or intradermally deliver the at least one substance.

Please replace paragraph [0059] with the following amended paragraph:

[0059] With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for the purposes of illustrative discussion of the preferred embodiment of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details

of the invention in more detail that is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several ~~form~~ forms of the invention may be embodied in practice.

Please replace paragraph [0071] with the following amended paragraph:

[0071] Patch 10 preferably further includes a skin attachment mechanism, which is preferably an adhesive layer 28 which serves for attaching patch 10 to a skin portion of the subject. Adhesive layer 28 covers at least a portion of bottom surface 13 of patch 10. Adhesive layer 28 preferably includes a biocompatible permeable pressure sensitive adhesive such as Bio-PSA from Dow Corning. ~~Coming~~. Other examples of biocompatible adhesives will be readily apparent to those of ordinary skill in the art. Adhesive layer 28 may be useful for either a single attachment or repeated attachments.

Please replace paragraphs [0073] and [0074] with the following amended paragraphs:

[0073] According to a preferred embodiment of the present invention electrochemical cell 14 is a thin flexible electrochemical cell, which engages most of the entire volume of patch body 11. In the presently preferred embodiment, electrochemical cell 14 includes a positive pole layer 16, a negative pole layer 18 and an electrolyte layer 20 interposed therebetween. An example of a suitable thin and flexible electrochemical cell is described, for example, in U.S. Pat. Nos. 5,652,043, 5,897,522 and 5,811,204, which are incorporated herein by reference. Briefly, the electrochemical cell described in the above identified U.S. Patents is an open liquid state, electrochemical cell which can be used as a primary or rechargeable power source for various miniaturized and portable electrically powered devices of compact design. The cell includes a first layer of insoluble negative pole, a second layer of insoluble positive pole and a third layer of aqueous electrolyte being disposed between the first and second layers and including (a) a deliquescent material for keeping the open cell wet at all times; (b) an electroactive soluble material for obtaining required ionic conductivity; and, (c) a water-soluble polymer for obtaining a required viscosity for adhering the first and second layers to the ~~first~~ third layer.

[0074] Several preferred embodiments of the disclosed electrochemical cell include (i) engaging

the electrolyte layer in a porous substance, such as, but not limited to, a filter paper, a plastic membrane, a cellulose membrane and a cloth; (ii) having the first layer of insoluble positive pole include manganese-dioxide powder and the second layer of insoluble negative pole include zinc powder; (iii) having the first layer of insoluble negative pole and/or the second layer of insoluble positive pole further include carbon powder; (iv) selecting the electroactive soluble from zinc-chloride, zinc-bromide, zinc-fluoride and potassium-hydroxide; (v) having the first layer of insoluble negative pole include silver-oxide powder and the second layer of insoluble positive pole include zinc powder and the electroactive soluble material is potassium-hydroxide; (vi) having the first layer of insoluble negative pole include cadmium powder and the second layer of insoluble positive pole include nickel-oxide powder and selecting the electroactive soluble material to be potassium-hydroxide; (vii) having the first layer of insoluble negative pole include iron powder and the second layer of insoluble positive pole include nickel-oxide powder and selecting the electroactive soluble material to be potassium-hydroxide; (viii) having the first layer of insoluble negative pole and the second layer, of insoluble positive pole include lead-oxide powder, then cell is charged by voltage applied to the poles and the electroactive soluble material is selected in this case to be sulfuric-acid; (ix) the deliquescent material and the electroactive soluble material can, be the same material such as zinc-chloride, zinc-bromide, zinc-fluoride and potassium-hydroxide; (x) the deliquescent material is selected from the group consisting of calcium-chloride, calcium-bromide, potassium-biphosphate and potassium-acetate; (xi) the water-soluble polymer can be polyvinyl alcohol, polyacrylamide, polyacrylic acid, polyvinylpyrrolidone, ~~polyvinylpyrrolidone~~, polyethylenoxide, agar, agarose, starch, hydroxyethylcellulose ~~hydroxyethylcellulose~~ and combinations and copolymers thereof; (xii) the water-soluble polymer and the deliquescent material can be the same material such as dextrane, dextranesulfate and combinations and copolymer thereof. Electrochemical cell 14 preferably incorporates any one or more of the embodiments described above. Preferred configurations for electrochemical cell 14 according to the present invention involve those combinations which are devoid of poisonous compounds.

Please replace paragraph [0079] with the following amended paragraph:

[0079] It is appreciated that each of electrodes 22 and 24 may be of any size and shape, and located with respect to one another, in any arrangement, as may be required to cover the skin portion under treatment. Indeed, in accordance with a preferred embodiment of the present invention, electrochemical cell 14, in conjunction with electrodes 22 and 24, constitute the sole internal elements of patch 10. Accordingly, patch 10 is among the smallest and thinnest active patches ~~practice~~ and delivers the maximum power per unit of surface area.

Please replace paragraph [0084] with the following amended paragraph:

[0084] In a presently preferred embodiment, the conductive fluid is electrically conductive and adhesive hydrogel, suitable for use as a skin contact adhesive and, particularly, suitable for use as an electrical interface for electrodes of medical devices. The hydrogels are cationic acrylates and may be, for example, preferably made from acrylic esters of quatarnary ~~quatemy~~ chlorides and/or sulfates or acrylic amides of quaternary chlorides. They can be formed by free radical polymerization in the presence of water, preferably by ultra-violet curing with initiator and multi-functional cross-linking agent. The hydrogel may preferably include a buffer system to help prevent discoloration of the hydrogels and/or hydrolysis of the hydrogels and/or to improve shelf-life.

Please replace paragraph [0089] with the following amended paragraph:

[0089] The conductive fluids used in conjunction with patch 10 are preferably administered by deposition on one or both electrodes. It is appreciated that the conductive fluid may alternatively or in addition be administered by topical application to the skin. The term "topical" is used herein to refer to administration of a substance on the surface of the skin or mucosal tissue, which can be applied via direct application (e.g., spreading), via an impregnated porous material or object or by spraying or misting. It will be appreciated that topical application of the fluid to the skin of the subject is typically less precise and, if not done carefully, may inadvertently cause an electrical connection between the electrodes directly through the conductive fluid such that the electric current and the mobilized ions would not pass through the skin.

Please replace paragraphs [0099]-[0101] with the following amended paragraphs:

[0099] Several foolproof embodiments with respect to patch 10 of the present invention are shown in FIGS. 3a-5c. In the embodiment of FIGS. 3a-d, a strip 100 is placed over the skin 102 and a conductive lotion, gel, cream or the like 104 is applied over the skin 102, such that upon removal of strip 100, two non-contacting zones 106 receptive of a patch 108 constructed and operative in accordance with the teachings of the present invention are formed and patch 108 is applied onto the skin 102, such that the electrodes 110 thereof each being in contact with one of zones 106 so as to avoid a ~~shortcut~~. short circuit.

[0100] In the embodiment of FIGS. 4a-d, a patterning device 200 having two openings 201 is placed over the skin 202 and a conductive lotion, gel, cream or the like 204 is applied over the skin 202, such that upon removal of patterning device 200, two non-contacting zones 206 receptive of a patch 208 constructed and operative in accordance with the teachings of the present invention are formed and patch 208 is applied onto the skin 202, such that the electrodes 210 thereof each being in contact with one of zones 206, so as to avoid a ~~shortcut~~. short circuit.

[0101] In the embodiment of FIGS. 5a-c, a foldable patch 308 is placed, in its folded configuration, over the skin 302 and a conductive lotion, gel, cream or the like 304 is applied over the skin 302 on both sides thereof, such that upon flattening patch 308, two non-contacting zones 306 receptive of patch 308 are formed and patch 308 is contacting the skin 302, such that the electrodes 310 thereof each being in contact with one of zones 306, so as to avoid a ~~shortcut~~. short circuit.

Please replace paragraph [0109] with the following amended paragraph:

[0109] The delivery of the substance transdermally or intradermally preferably occurs by a process of iontophoresis and/or electrophoresis. ~~Iontophoresis~~ Iontophoresis refers to the movement of ions caused by the application of an electrical potential. Electrophoresis refers to the movement of charged colloidal particles or macromolecules caused by the application of an electrical field. The electric current caused by the electric potential between electrodes 22 and 24 serves to release the charged substance from the conductive fluid and to deliver the

molecules/ions of the charged substance from the conductive fluid and to deliver the molecules into the adjacent skin tissue. The charged substance within the conductive fluid, which is deposited between one or both of electrodes 22 and 24 and the skin of the subject, would be attracted to or repelled by electrode 22 and electrode 24 as appropriate to their charge. For example, if the substance is positively charged, electrode 22 would repel the substance, thus mobilizing it into or through the skin. In this configuration, when current flows from positive electrode 22 in a direction toward the skin, the charged substance is driven across the conductive fluid/skin interface into the skin.

Please replace paragraph [0164] with the following amended paragraph:

[0164] As described above and found insofar also in the pertaining trade [[5]] literature (refer to book "Elektrische Differential-Therapie" [Electrical Differential Therapy] by A. Hansjuorgens and H. U. May, 1990; Nemectron GmbH, Karlsruhe), the prior electrotherapeutic apparatuses employ, depending on diagnosis, low-frequency currents or amplitude-modulated medium-frequency currents at frequencies >0 to 200 Hz or medium-frequency currents at a frequency of >5 Hz to 100,000 Hz, each with constant amplitude (intensity).

Please replace paragraph [0171] with the following amended paragraph:

[0171] Additional objects, advantages, and novel features of the present [[a]] invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of they present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

Please replace paragraphs [0173] and [0174] with the following amended paragraphs:

[0173] Mild rosacea, characterized by redness of parts of the face and telangectasia, is a common disorder, afflicting many individuals, mainly from the aging population. Unfortunately the treatments for mild rosacea are [[5]] limited.

[0174] Three patients with mild rosacea were enrolled in a pilot study, ~~meting~~ meeting the following inclusion criteria:

Please replace paragraph [0181] with the following amended paragraph:

[0181] Each patch was coated by a Test Preparation (aqueous gel, containing witch hazel extract). 0.4 ml of the Test Preparation was evenly applied onto the Main Patch and 0.1 ml to the Counter Patch, using a spatula. The patches were then applied onto the skin of the study subjects for a [[5]] period of 7-20 minutes (the Treatment Period).